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10/006,205	12/10/2001	Christa Tauer	V-258.00	9038

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/09/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	10/006,205	TAUER ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *15-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-51 are pending.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-14 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that Groups I and II should be examined together since they are in the same classification.

2. Applicants' argument has been respectfully considered. First examiner apologizes for placing group II is a wrong classification. However, applicants are reminded that the classification is not only criteria for the ***Election/Restriction*** requirement, there are so many other issues that need to be considered, even the two claimed inventions are classified in the same classification, they may required complete different searches. For example, the method of Group II is for isolating the purified mature HAV virions, whereas the method of Group I is for complete HAV particles purification. Because the complete HAV particle and mature HAV virion differ in structures and other physical characteristics, such as density, which need different procedures for the purification. Therefore, the two groups of inventions require different searches and constitute patentable distinct inventions.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claims 1-14 are considered.

5. Applicants are required to cancel the claims 15-51 drawn to the non-elected groups.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the HAV preparation is made in claim 1, is it by centrifugation or filtration? How many filtering steps are involved from claims 1-11, especially, when the exactly filtration(s) is conducted and, what the size of the filter(s) is used <u>for each filtering steps</u> and what concentrations and incubation times of a DNase and each of proteases

are used for the degrading procedure etc. These are all essential steps required for making the purified HAV particles by the claimed method in order to reach to the purity and yield as what it is claimed in claims 12 and 13.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a method of producing the purified complete hepatitis virus A particles at the concentration of 5000IU of HAV antigen/mg protein with purity of 30 pg contaminating nucleic acid/IU HAV antigen by using a filtration method plus the degradation treatment with a purified Streptomyces griseus trypsin (SGT), does not reasonably provide enablement for producing the same high yield of HAV particles by using any other microbial protease as it is claimed in claims 6 and 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

10. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

11. 1) & 2) State of art and Unpredictability. The state of art teaches that trypsin used as a protease is required during the purification of HAV in order to degrade the contaminated host cellular protein.

12. However, It is unpredictable that any or all microbial protease, such as pronase or any fraction of pronase will fulfill the same function for degrading the contaminated host cellular protein without destroying the structure and antigenicity of the virus. Because pronase is a mixture of many different enzymes, it can cleave some structural proteins from a virus. For example, MiKim-Breschkin et al. (J. Virol. Methods 1991, Vol. 32, pp. 121-124) teach that the mixture pronase is used for cleaving the neuraminidase (NA) heads from influenza A virus (See lines 19-28 on page 122).This unpredictability is also addressed by Applicants own disclosure (See lines 8-10 of paragraph of 046 on page 12). The specification states that pronase is a mixture of many enzymes, one of the enzymes in the mixture of pronase may have other function that may bring an adverse effect on the HAV preparation.

13. Moreover, some enzymatic fractions of pronase are peptidases, such as aminopeptidases, as evidenced by Yokosawa et al. (J. Biochem. 1976, Vol. 79, pp. 757-763, see the first paragraph on page 757), which are only suitable for cleaving short peptide and are not suitable for degrading contaminated cellular proteins with heavy molecular weights.

14. Therefore, it is unpredictable of using any or all microbial protease or any enzymatic fractions of pronase to produce the same high yield of purified complete HAV protein particles.

15. 3) & 4) Number of working examples and Amount of guidance. The specification teaches that purification of complete HAV particles is done by digestion with 0.5-5 U/ml of SGT for 24 hours at room temperature. However, the specification presents no working examples of using any or all microbial protease, such as pronase or other enzymatically active fraction of pronase, such as aminopeptidases, other than SGT for purification of HAV particles.

16. 5) Scope of the claims. The claims broad read on a method of producing the complete HAV particle at 5000 IU of HAV antigen/mg proteins with purity of 30 pg contaminating nucleic acid/IU HAV antigen by using any or all microbial protease or pronase or any faction of enzymatically active fraction of pronase.

17. 6) & 7) Nature of the invention and lever of the skill in the art. While the general technique for purifying HAV particles is known, it still requires an adequate disclosure and guidance for a person skill in the art to practice the full scope of claimed invention .

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that without adequate

teaching an disclosure, the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1-5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (US Patent SN. 5,268,292A).

20. Robertson et al. teach a method for generating hepatitis A virus (HAV) particle involves the steps of growing HAV in the FrhK4 cells; harvesting the complete HAV viral particles; and concentrating the viral particle by ultrafiltration with a hollow fiber filter having a cut off size at 100,000 MW (See lines 40-43 on col. 5) followed by treating the concentrated viral particle with DNase and trypsin respectively (See lines 54-59 on col. 5). The enzyme-treated HAV particles are concentrated and purified with a Centriflo cone filter unit through centrifugation effort, wherein the cut off size of Centriflo cone filter is at 25,000 MW (See lines 18-20 on col. 6). Because the physical isolating processes of HAV particle taught by Robertson et al. are mainly involved filtrations, the HAV virus particles are considered to be isolated by filtering, which meet the limitation of claims 3 and 11 (See line 9 on col. 5 through line 25 on col. 6). Because the trypsin is one of proteases, it meant the limitation of claim 2. Therefore, the claimed invention is anticipated by the cited reference.

21. Claims 1-2, 4-5 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuzuhara et al. (EP 0 339 667B1).

22. Kuzuhara et al. teach a method for isolating HAV viral particle comprises steps of (1). Harvesting the infected HAV particle from the infected cells by centrifugation; (2). Treating the HAV virus particle preparation with DNAsa I; and then Proteinase K; (3). Concentrating the virus particle in solution by centrifugation; (4). Purifying the HCV particle containing fraction by

a gel filtration column; (5). Sterilizing the positive fraction by filtration and (6). Finally, inactivating the purified HAV virus with formalin (See Section of Reference Example 1: Cultivating and Purification of HAV on page 4 and 5). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 1-5, 9-11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (US Patent SN. 5,268,292A), Provost et al. (US Patent No. 4,783,407), Kistner et al. et al. (WO 96/15231A2), Cinatl Jr. et al. (Biology International 1993, Vol. 17, No. 9, pp. 885-895) and Kuzuhara et al. (EP 0 339 667B1).

25. Claimed invention is directed to a method for producing complete hepatitis A virus (HAV) particles from a cell culture, preferably, from a Vero cell line with a serum free or protein free medium, comprising the step of concentrating cell culture supernatant containing the viral particle, preferably by filtration; treating the virus preparation with a DNAse and a protease. The final step of the preparing the HAV particle is to inactivate the viral particle by an inactivating agent.

26. Robertson et al. teach a method for generating high yield of hepatitis A virus (HAV) particle involves the steps of growing HAV in the FrhK4 cells; harvesting the complete HAV viral particles; and concentrating the viral particle by ultrafiltration with a hollow fiber filter having a cut off size at 100,000 MW (See lines 40-43 on col. 5) followed by treating the concentrated viral particle with a DNase and a trypsin enzymes respectively (See lines 54-59 on col. 5). The enzyme-treated HAV particles are then concentrated and purified with a Centriflo cone filter by force of centrifugation, in which the cut off size of Centriflo cone is at 25,000 MW

(See lines 18-20 on col. 6). Because the physical isolating processes of HAV particle taught by Robertson et al. are mainly involved filtration, the HAV virus particles are considered to be isolated by the filtering, which meet the limitation of claims 3 and 11 (See line 9 on col. 5 through line 25 on col. 6). Robertson et al. do not teach that the HAV particles are prepared from the Vero cell culture in serum free or protein free medium.

27. However, it is already known in the art prior to the current invention was filed that Vero cell is not only susceptible for propagating HAV, which exhibits a great advantage over other cell lines used in the art as evidenced by Provost et al, but also grows very well in a serum free or protein free medium when it is used for producing virus as evidenced by Kistner et al. (WO 96,15231A2).

28. For instance, Provost et al. explicitly teach a method for using Vero cell to grow HAV, and they also disclose that the use of Vero cell has great advantage over other acceptable cell lines because Vero cells are available in large quantities and more readily adaptable to large scale cell culture technique than MRC-5 cells since the transformed Vero cell line has an infinity lifetime and will always be adequate for large-scale vaccine manufacture (See examples 1 and 2 on col. 3 & 4 and lines 34-45 on col. 1 and). Kistner et al. disclosed that Vero cell line is licensed by WHO for general vaccine production and it susceptible for growing many viruses, including HAV in the serum and protein free medium (Claims 1-4). In addition, Kistner et al. further point out that the advantage of using serum free medium is to overcome the problem of lacking batch-to-batch consistency, and undesired contaminations by using the serum containing medium that complicates the viral production and purification process (See lines 32 on page 11 through line 5 on page 12).

29. In addition, prior art as evidenced by Cinatl Jr. et al. also explicitly teaches the formulation of a protein-free medium (PFEK-1) (The medium is serum free too) and condition of using PFEK-1 to culture Vero cells for producing viruese (See entire section of MATERIALS AND METHODS, especially, Table 1 on page 887-889). Especially, Cinatl Jr. et al. concluded that Vero cells can proliferate in PFEK-1 medium to the similar extent as cells in serum-supplemented medium and all viruses produced by the Vero cells in the PFEK-1 medium had similar virus titers to those cultured in serum-containing medium (See Abstract).

30. Regarding to the HAV inactivation, it is so well known in the art prior to the current invention was filed that the formalin is used for activation of HAV, and the inactivated HAV is used as vaccine as evidenced by Kuzuhara et al. (See lines 16-18 on page 5).

31. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references to generate the purified HAV particles by combining all well established methods in the art as described above and inactivate the HAV particles with formalin without unexpected result.

32. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

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While claims 8 and 12-13 are deemed free of prior art and rejection, given failure of the prior art to teach or reasonably suggest a method for particularly using Streptomyces griseus trypsin isolated from microbial pronase to purify the complete HAV particle, which enable the virus preparation to reach the high yield at least about 5000 IU of HAV antigen /mg protein with purity of less than about 30 pg contaminated nucleic acid/IU HAV antigen. However, the claims are not in the condition for allowance because they are dependent on the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li Auguste 15 2003